Advances in the Therapy of Waldenstrom's Macroglobulinemia.

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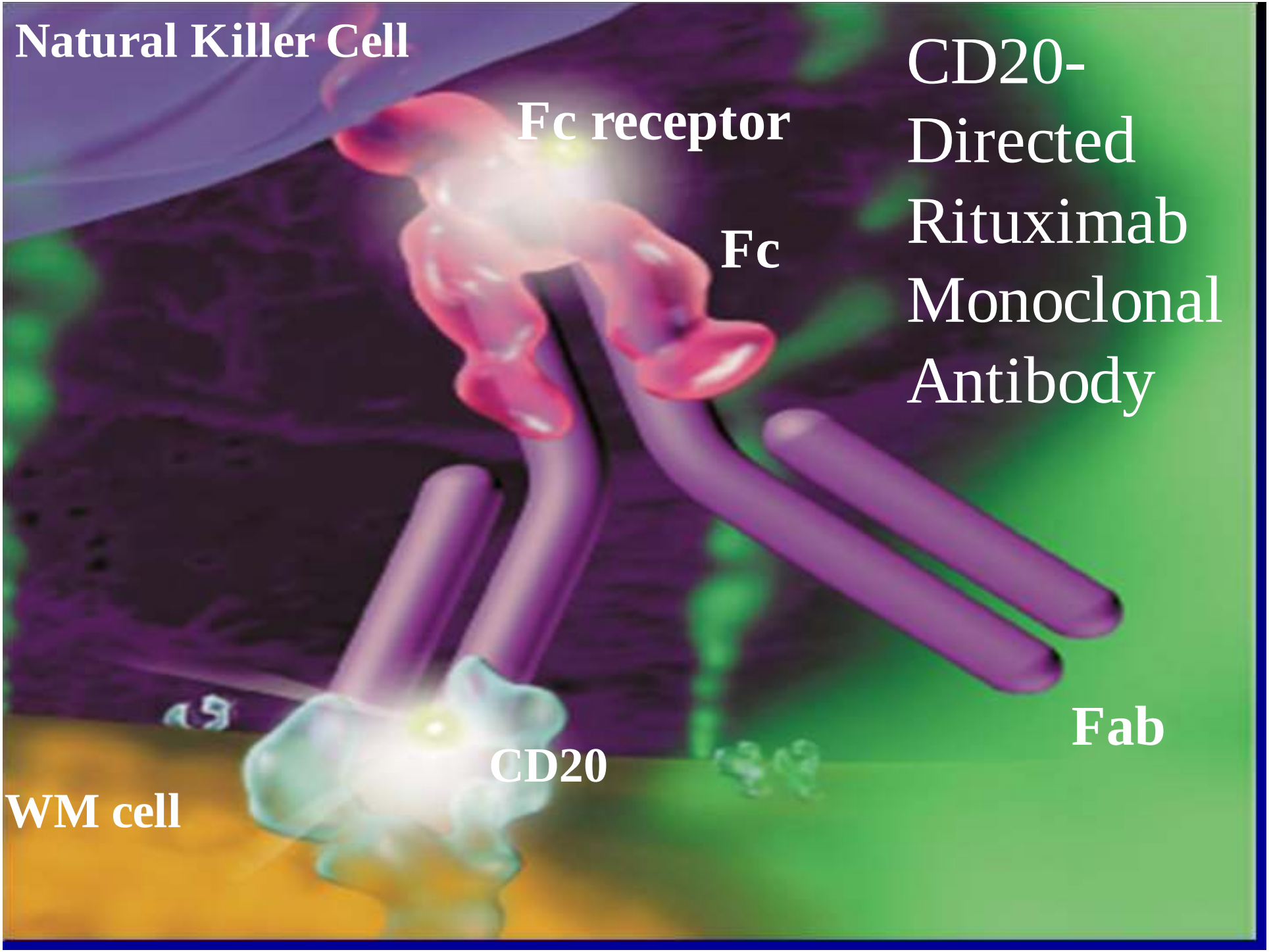
3rd International Workshop on Waldenstrom's Macroglobulinemia

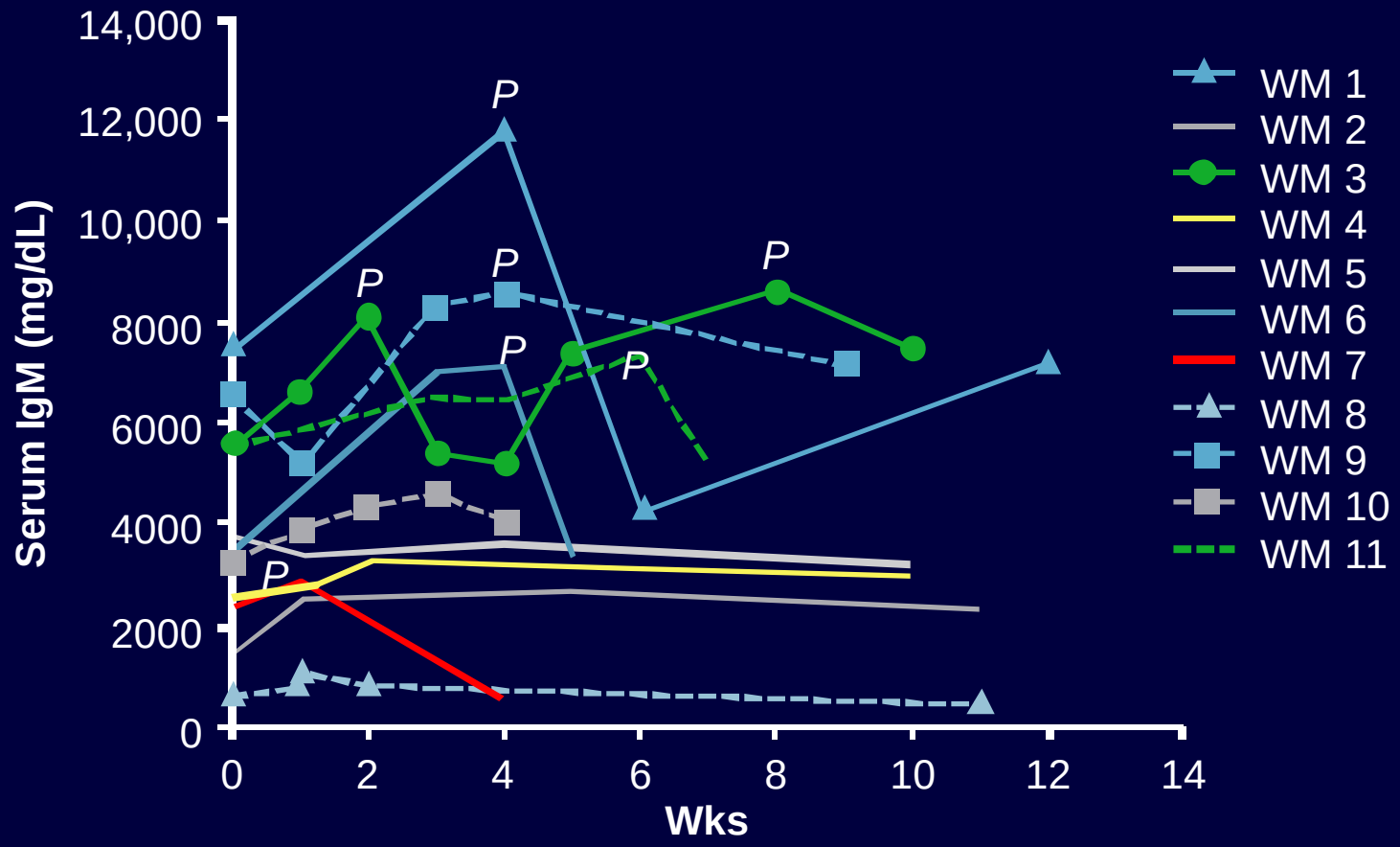
Paris, 2004

7th International Workshop on Waldenstrom's Macroglobulinemia

Newport, RI, USA
www.wmworkshop.org
August 2012


Natural Killer Cell
Fc receptor
Fc
CD20-
Directed
Rituximab
Monoclonal
Antibody
Fab
CD20
WM cell

Serum IgM Levels Following Rituximab in Patients With WM



P denotes patient-required plasmapheresis for hyperviscosity.

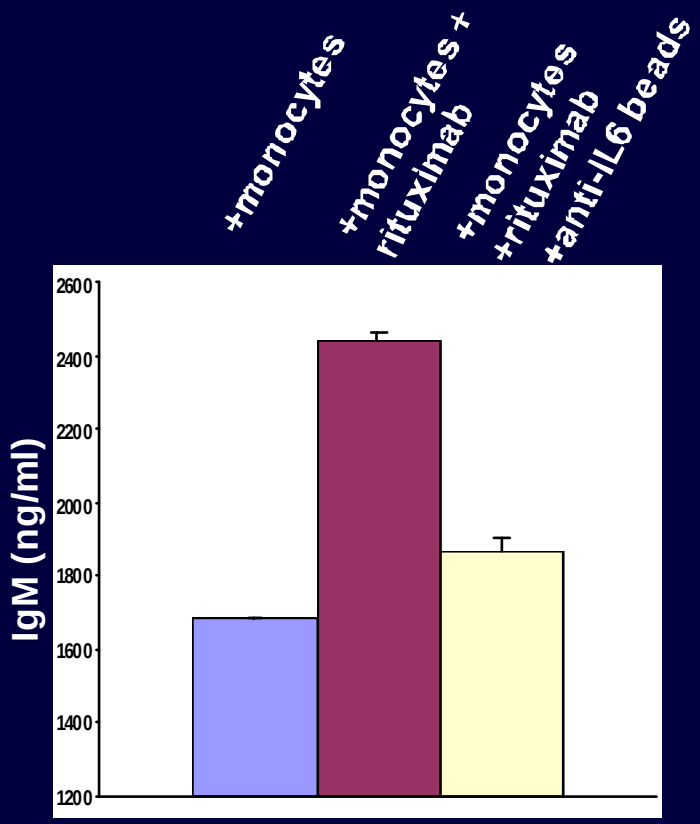
Treon SP, et al. Ann Oncol. 2004;15:1481-1483.

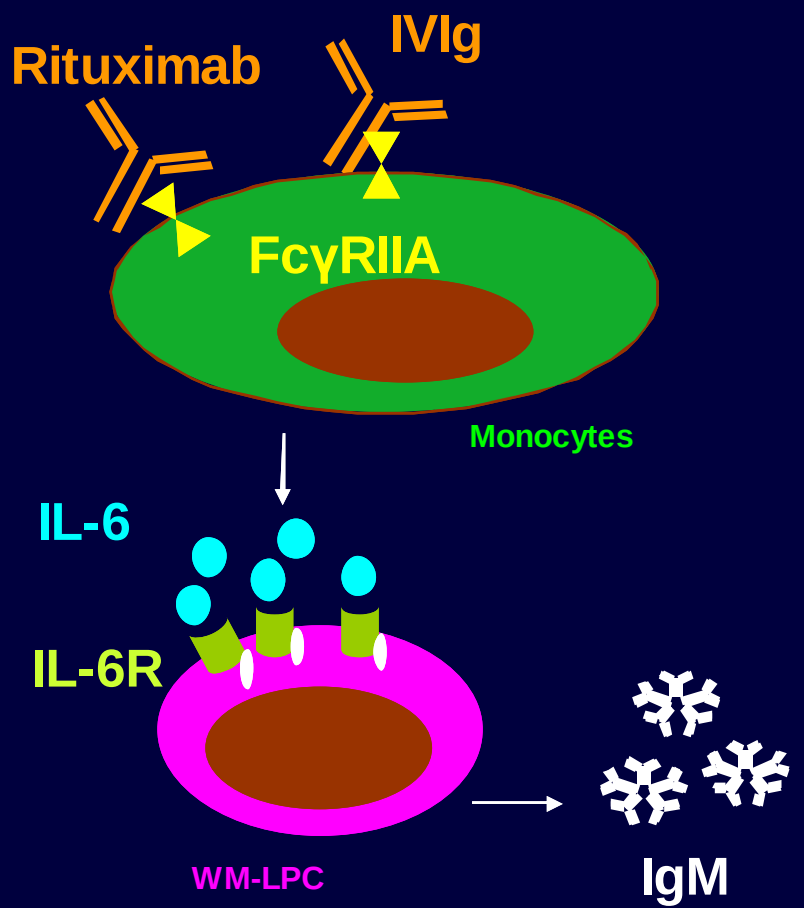
Rituximab induced IgM flare occurs in patients receiving combination therapy.

- Monotherapy (60%)
- Fludarabine/Rituximab (40%)
- Cyclophosphamide/Rituximab (30%)
- Thalidomide/Rituximab (50%)
- Lenalidomide/Rituximab (75%)
- Bortezomib/Dexamethasone/Rituximab (9%)
- Bortezomib/Rituximab (20%)

Treon et al, Ann Oncol 2004; Nichols et al, ASH 2004; Ioakimidis et al, Clin Lymphoma Myeloma 2009; Treon et al, Blood 2008; Treon et al, Clin Cancer Res 2008; Treon JCO 2009; Ghobrial et al, ASH 2009.

Bystander release of IL-6 by Monocytes may account for the Rituximab IgM flare.





Primary Therapy of WM with Rituximab Based Options

Regimen	ORR	CR
Rituximab x 4	25-30%	0%
Rituximab x 8	40-45%	0%
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, RCD	70-80%	8-10%
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	5-10%
Rituximab/thalidomide	70%	5%
Rituximab/bortezomib i.e. BDR, VR	70-90%	10-25%
Rituximab/bendamustine	90%	NA

Disease transformation and MDS/AML following nucleoside analogues in WM

Study	Population	N=	Median F/U (mo)	Outcome
Leleu et al, JCO 2009	Prev treated with NA vs. non-NA or untreated	439	60	Histological Transformation (8%) MDS/AML (5%)
Tamburini et al, Leukemia 2005	Firstline with Fludara/Cyclo	49	41	Histological Transformation (10%)
Leblond, JCO 1998	Previously treated with Fludara	71	34	Histological Transformation (10%)
Rakkhit et al, ASH 2008	Untreated; 2CDA based therapy	111	NA	Histological Transformation (9%)

Thalidomide and Rituximab in WM

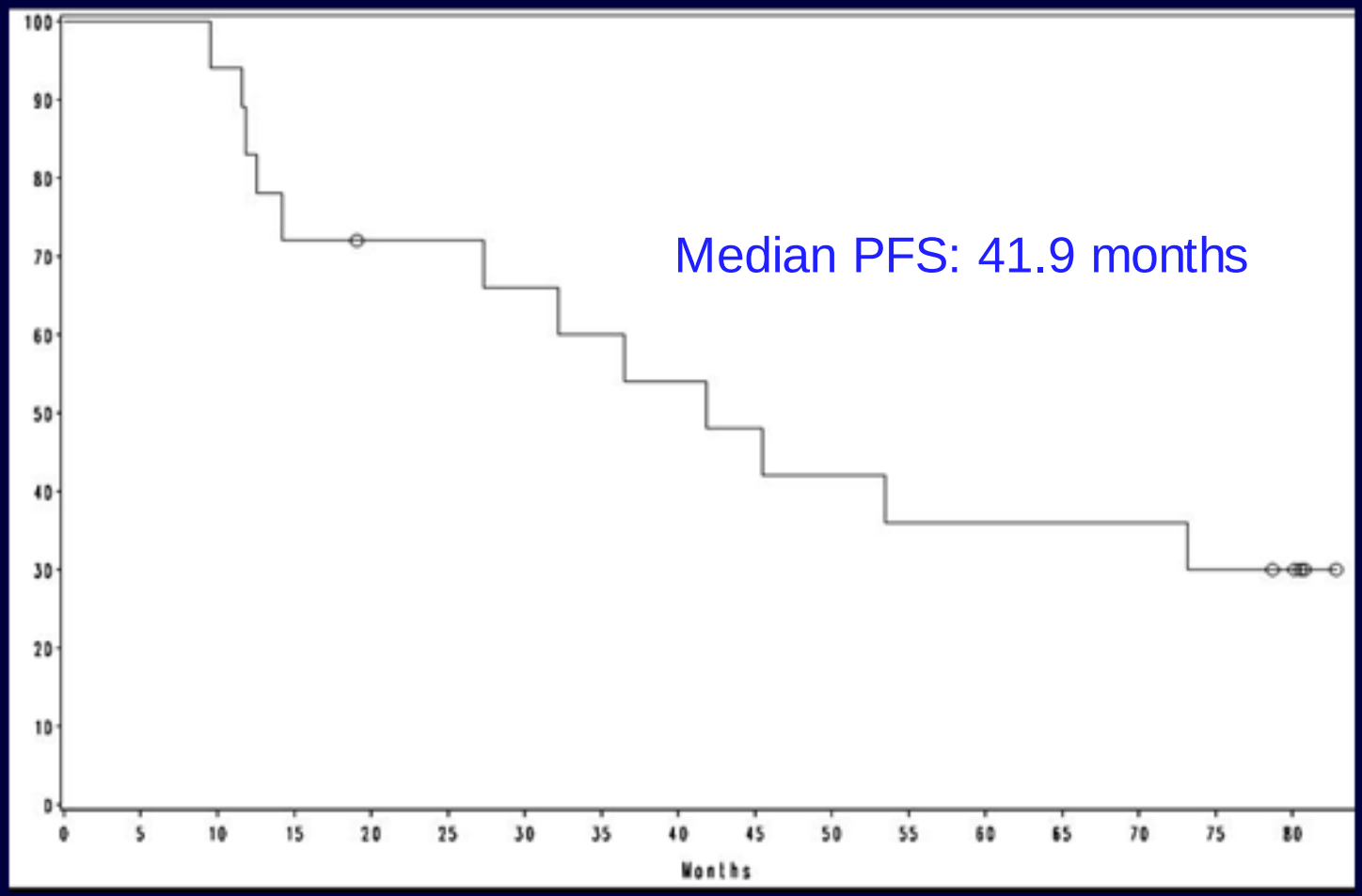
- N=25
- Thalidomide at 200 mg, increase to 400 mg and 8 infusions (375 mg/m^2 per week) of rituximab.
- ORR: 72%; CR/VGPR: 4%
- Short-term toxicities included:

  Sensory neuropathy (11); resolved grade 1 or less: 10.

  Confusion (3), tremors (2), bradycardia (2).
- Dose reduction in all pts. 50-100 mg/day tolerated.

Blood 2008; 112:4452

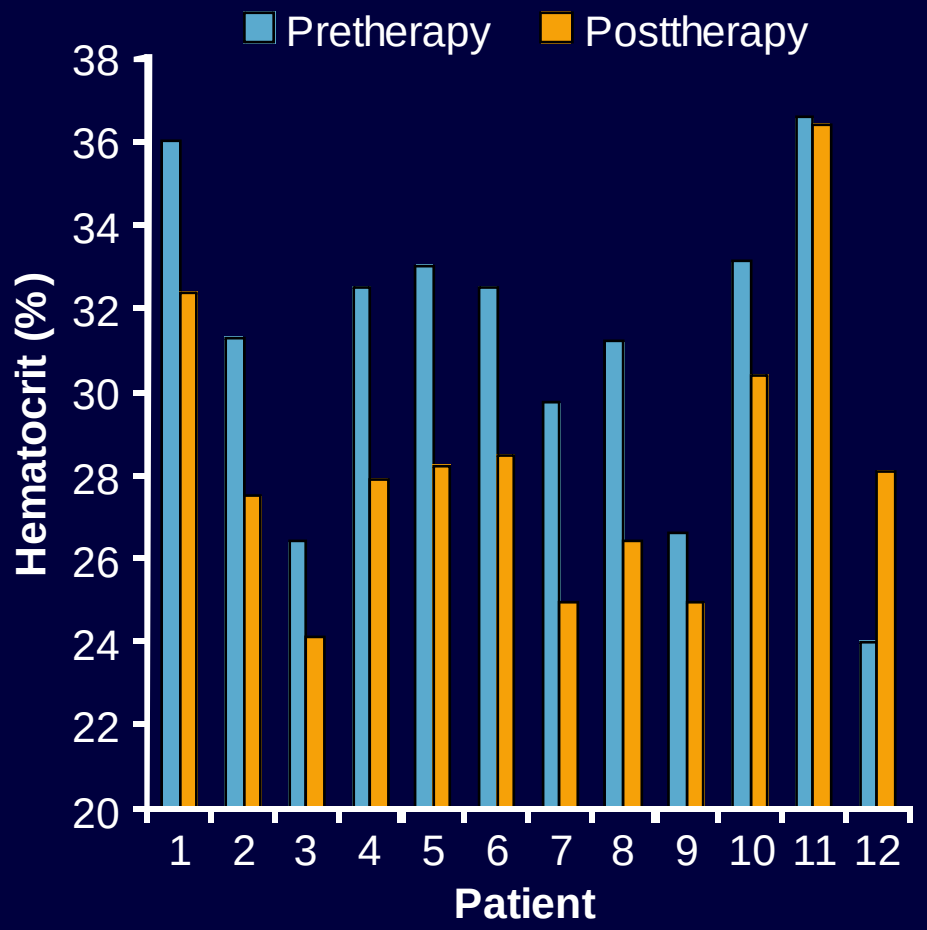
Thalidomide and Rituximab in WM



Median Follow-up: 40.4 months

Lenalidomide (Revlimid)-Induced Anemia in WM

- Decreased Hct observed in 10/12 pts following first week of lenalidomide monotherapy
- Median Hct decrease: 3.9% (31.9% to 28.0%; *P* = .003)
- No evidence for hemolysis; concurrent thrombocytopenia observed in 1 pt
- 4 patients hospitalized for anemia related complications (Afib, syncope, CHF)



Treon SP, et al. Clin Cancer Res 2008

Phase I Study of Pomalidomide, Dexamethasone, Rituximab (PDR) in WM.

Pomalidomide	1,2,3,4 mg QD	52 weeks
Dexamethasone	40 mg wkly IV	pre-Rituximab
Rituximab	375 mg/m2/wk	W1-4; W12-15.

Proteasome Inhibitors

Bortezomib combination therapy in WM

- **Primary**

  Bortezomib (1.3 mg/m^2/biwkly)/Dexamethasone/Rituximab

  ORR 95%; CR 22%; TTP >3 yrs; 30% Grade 3 PN

  Bortezomib (1.6 mg/m^2/wk)/Rituximab

  ORR 92%; CR 8%; 80% 1 Y PFS; No Grade 3 PN

- **Salvage**

  Bortezomib (1.6 mg/m^2/wk)/Rituximab

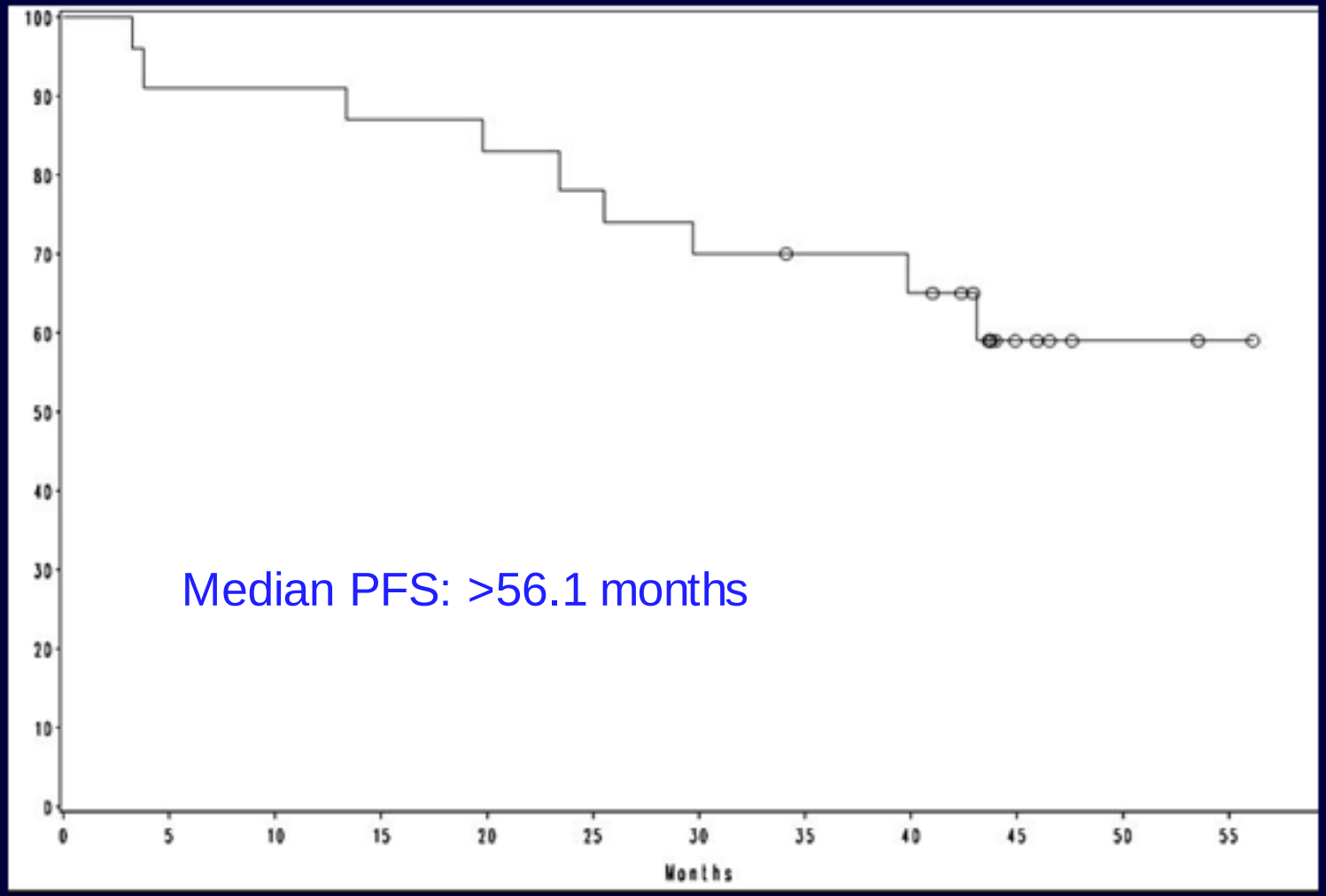
  ORR 81%; CR 5%; TTP 12 mos; 5% Grade 3 PN.

  Bortezomib (randomized wkly vs. biwkly)/Rituximab

  ORR 80%; CR 0%; TTP ?; 0% Grade 3 PN.

Treon et al, JCO 2009; Ghobrial et al, AJH 2010; Ghobrial et al, JCO 2010; Agathocleous et al, ASH 2007

Bortezomib, Dexamethasone and Rituximab



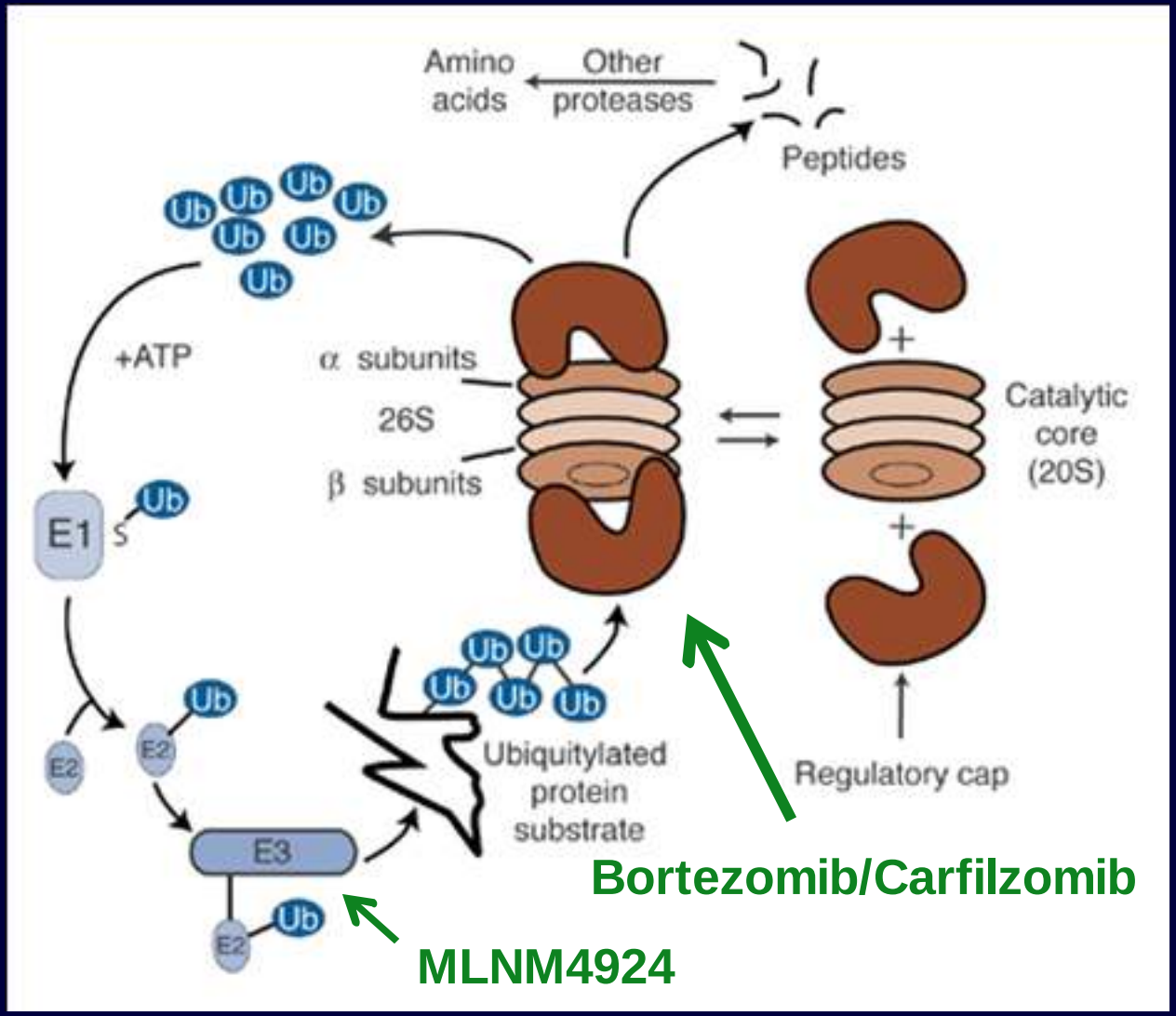
Median Follow-up: 43.3 months

IWWM6, Venice 2010

Bortezomib-Based Rituximab Therapy

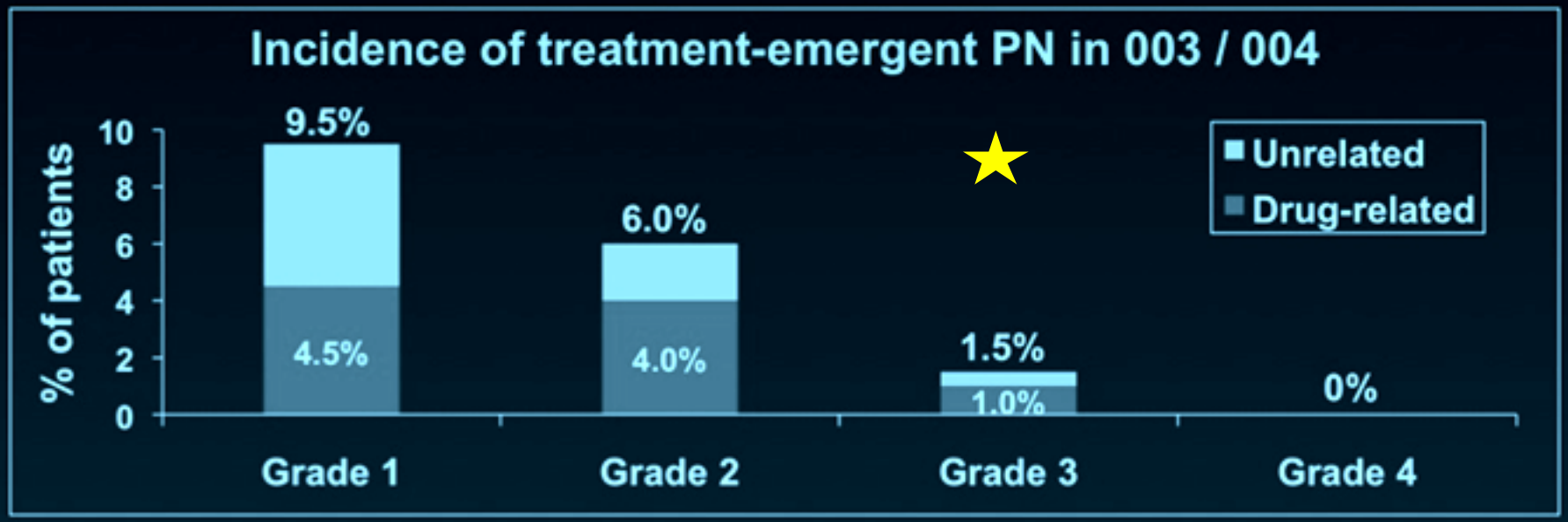
Twice A Week	Once A Week
↑ CR/VGPR	↓ Neuropathy
↑ PFS (?)	
↓ Time to Response	
↓ Rituximab IgM Flare	

Proteasome: Cellular Recycling Plant



Neuropathy Data for Carfilzomib in MM (Pooled Data from 003/004 Studies)

	N=201
Prior history of neuropathy	**155 (78%)**
Related to prior treatment	122 (61%)
Neuropathy symptoms at baseline	**109 (54%)**



***Only 1 patient had drug discontinued for PN** (study 004; BTZ-treated arm)*

Wolf JL, et al. ASCO 2010. Abstract 8135 (poster presentation).

Primary Therapy of WM with Carfilzomib, Rituximab, Dex (CARD)

Induction Cycle 1 q21 days

Days 1,2,8,9 Carfilzomib 20 mg/m^2 IV; Dexamethasone 20 mg IV.

Days 2,9 Rituximab 375 mg/m^2

↓

Induction Cycle 2-6 q21 days

Days 1,2,8,9 Carfilzomib 36 mg/m^2 IV; Dexamethasone 20 mg IV.

Days 2,9 Rituximab 375 mg/m^2

↓

2 months

Maintenance Cycles 1-8 q 2 months

Days 1,2 Carfilzomib 36 mg/m^2 IV; Dexamethasone 20 mg IV.

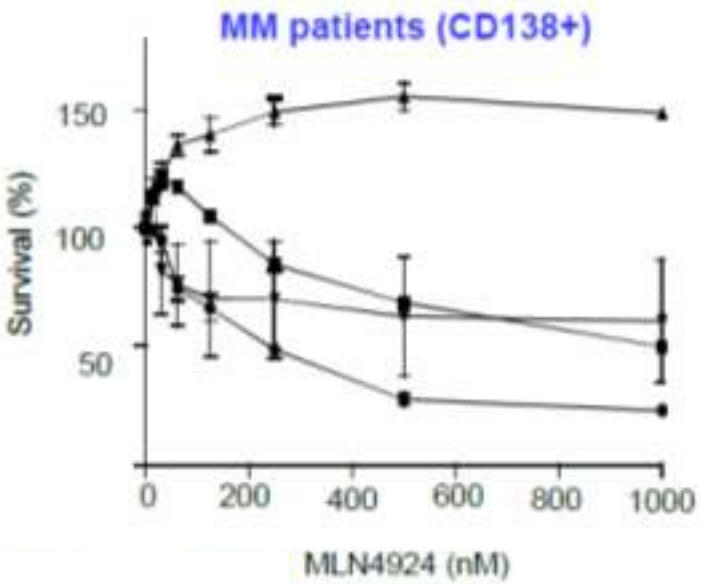
Days 2 Rituximab 375 mg/m^2

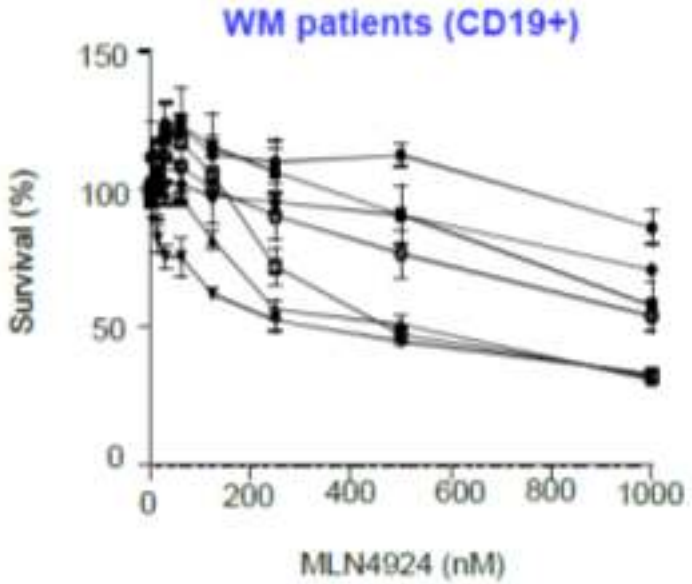
MLN4924: preclinical studies

In vitro effects of MLN4924 against MM and WM

MLN4924 was active against primary MM and WM patient samples at sub-micromolar levels

- The majority of CD138+ MM pt samples were responsive to MLN4924 at doses <500 nM
- 50% of CD19+ WM pt samples were responsive at doses <500 nM





McMillin DW, et al. ASCO 2010, Chicago, IL, USA (abstract 8110)
Data from poster presentation

MLNM 4924 /Dexamethasone in Relapsed/Refractory WM

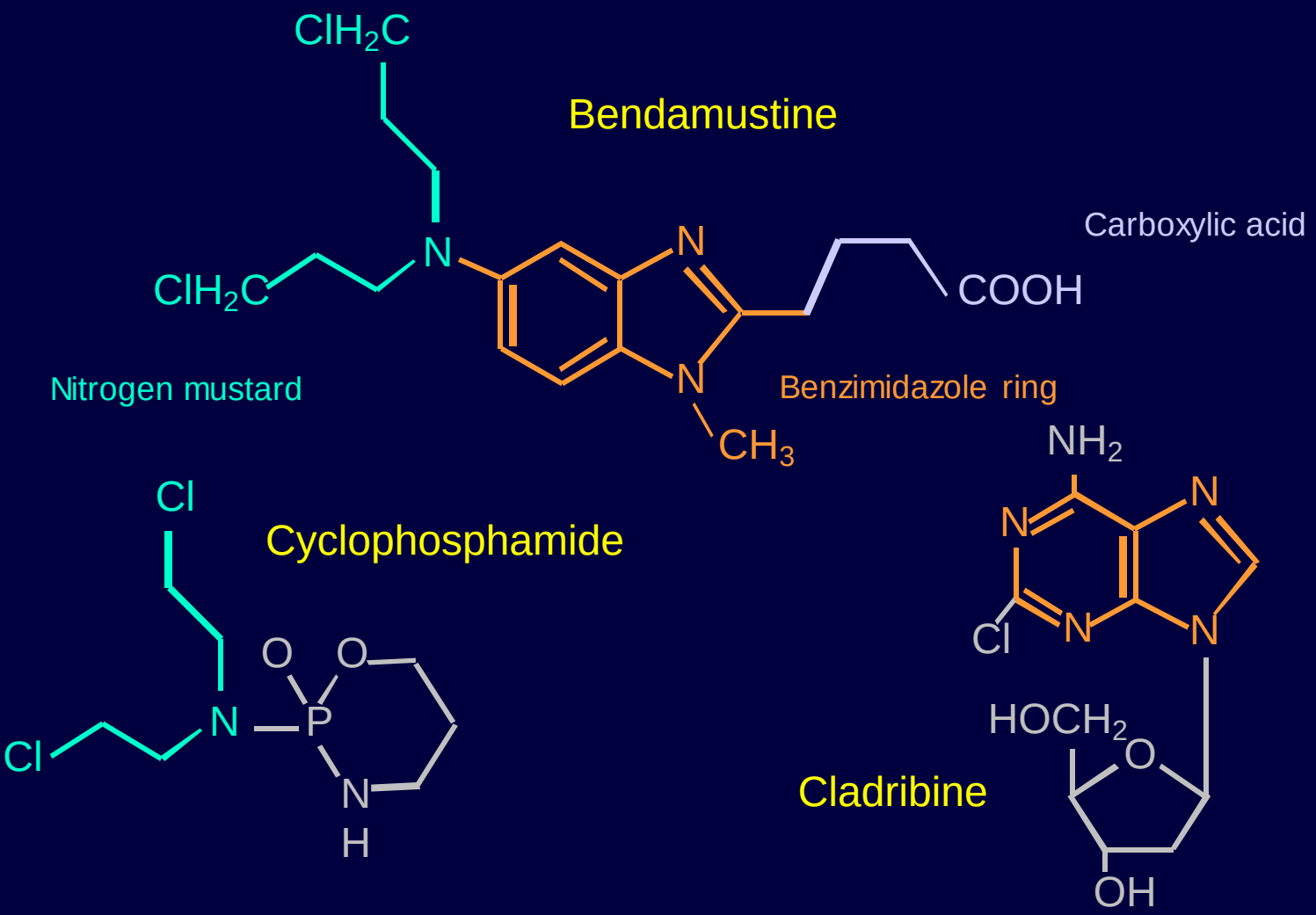
Induction Cycle 1 q21 days
Days 1,4,8,11 MLN 4924 20 mg/m^2 IV; Dexamethasone 20 mg IV.

Induction Cycle 2-6 q21 days
Days 1,4,8,11 MLN 4924 20 mg/m2 IV; Dexamethasone 20 mg IV.

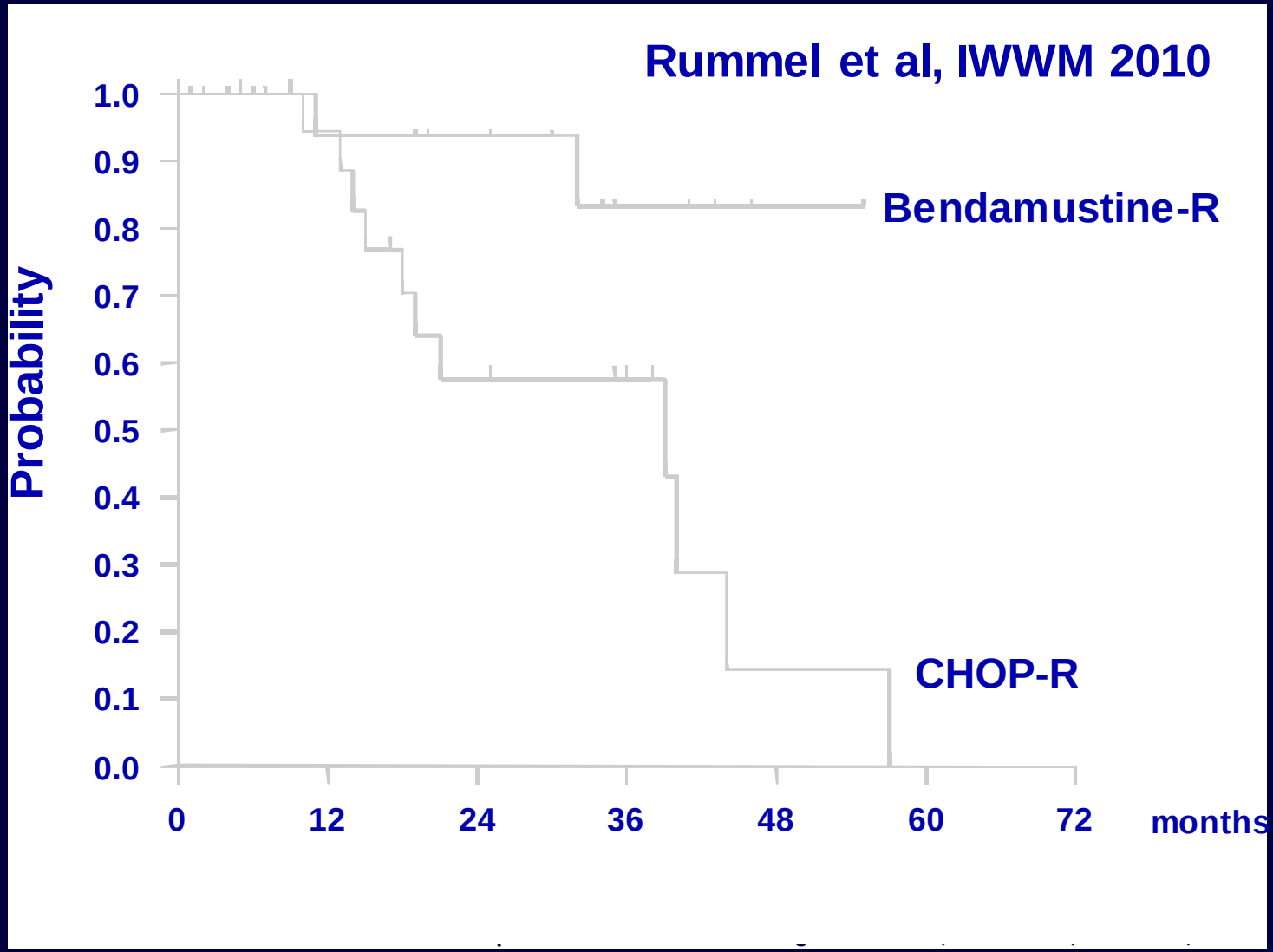
2 months

Maintenance Cycles 1-6 q 2 months
Days 1,4,8,11 MLN 4924 20 mg/m2 IV; Dexamethasone 20 mg IV.

Bendamustine

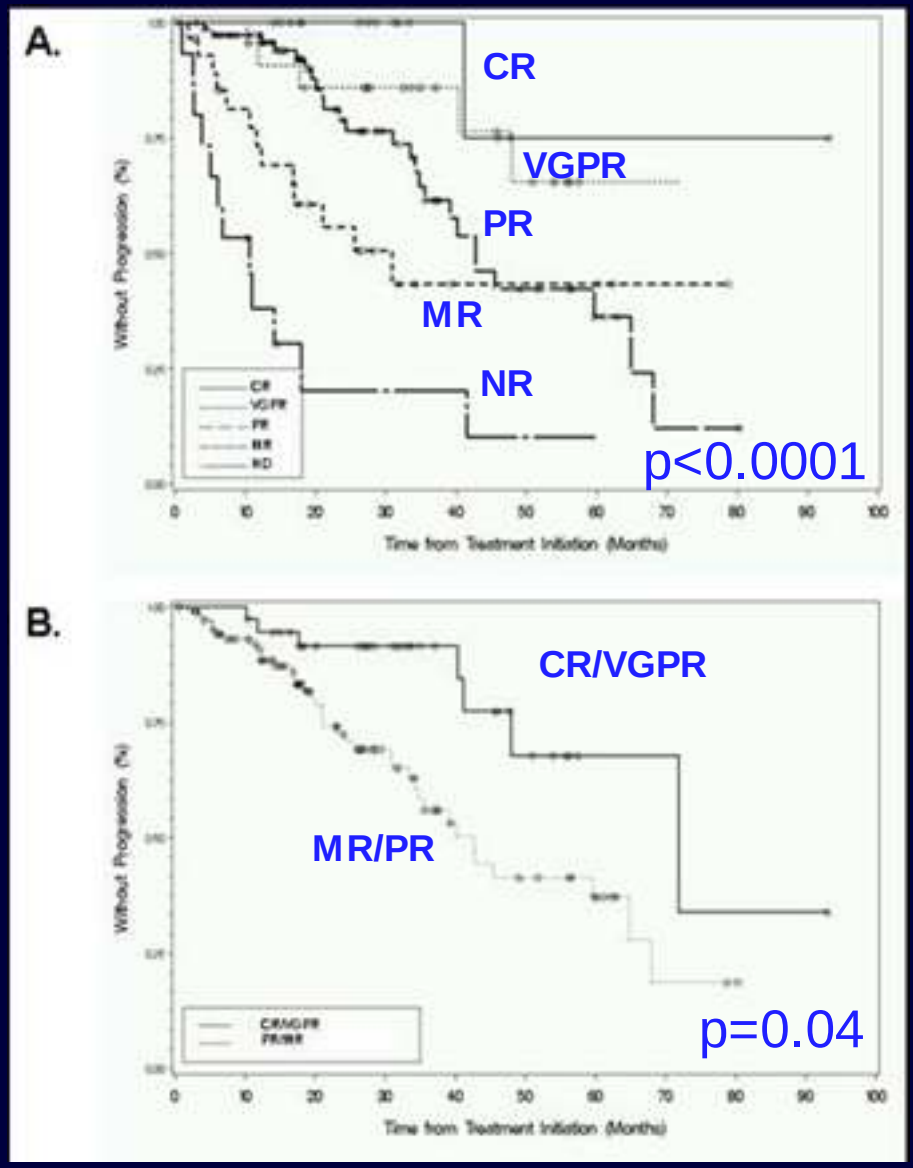


PFS: Benda-R vs CHOP-R in frontline WM

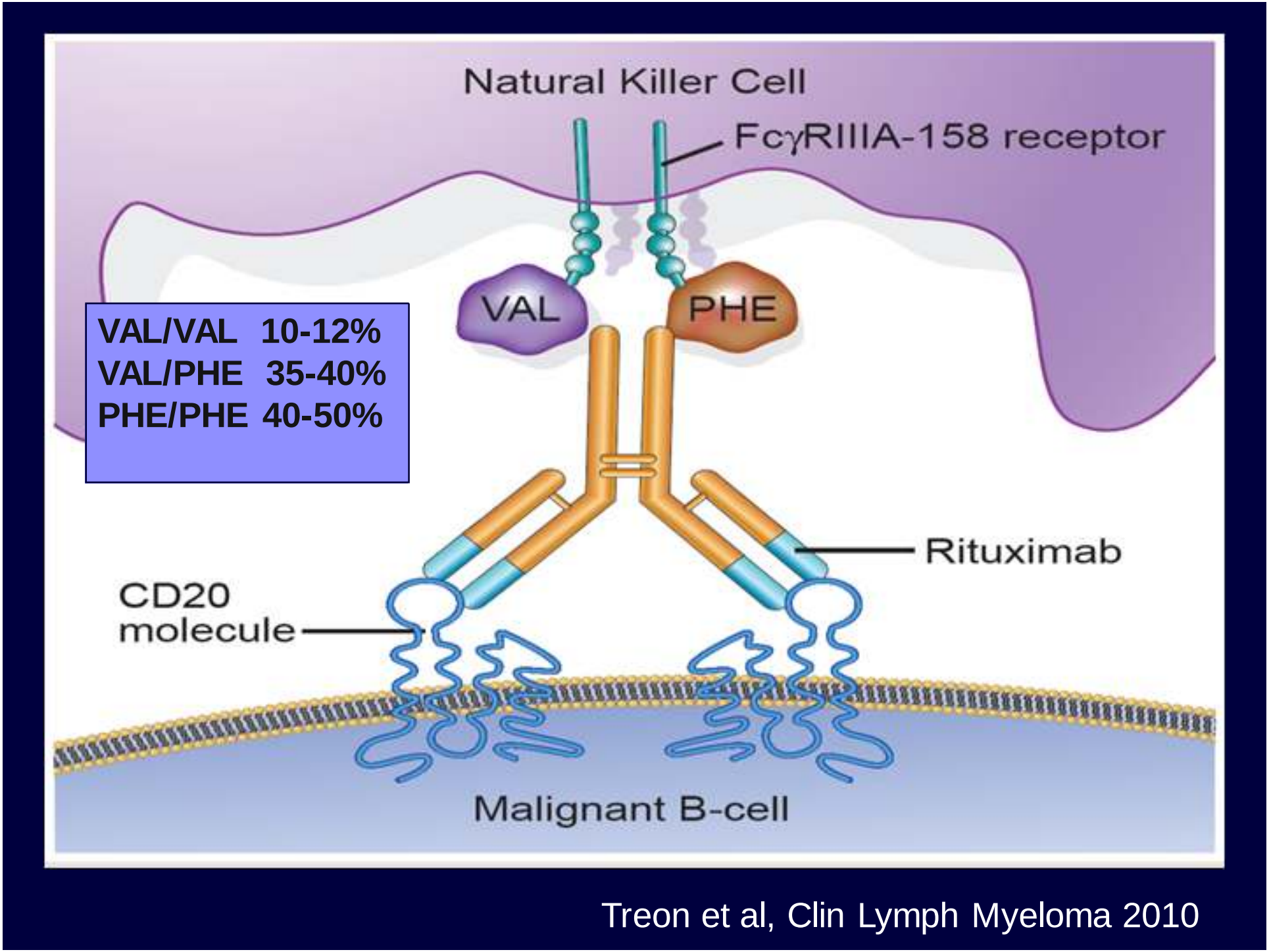


PFS in rituximab naïve WM pts treated with rituximab based therapy (n=159).

Response	Estimated PFS (mo.)
CR	>90
VGPR	>75
PR	42.6
MR	30.8
NR/SD	10.6

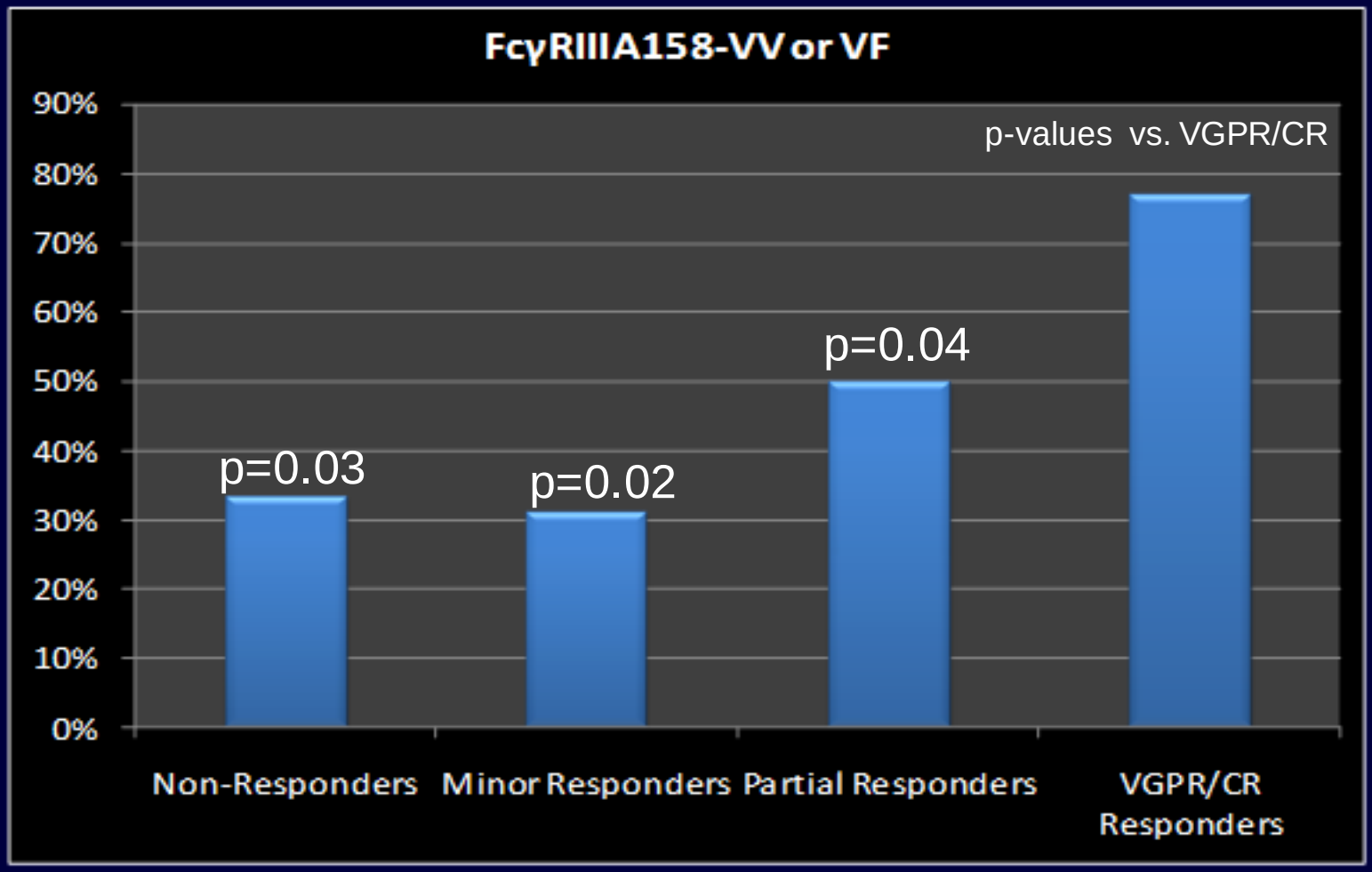


Treon et al, BJH 2011



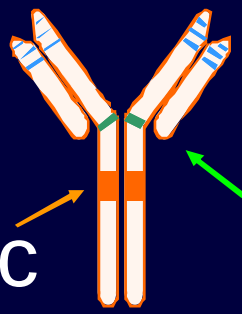
Treon et al, Clin Lymph Myeloma 2010

FcγRIIIA-158 polymorphisms predict response in WM



Treon et al, BJH 2011

GA101: Novel Humanized CD20 MAB



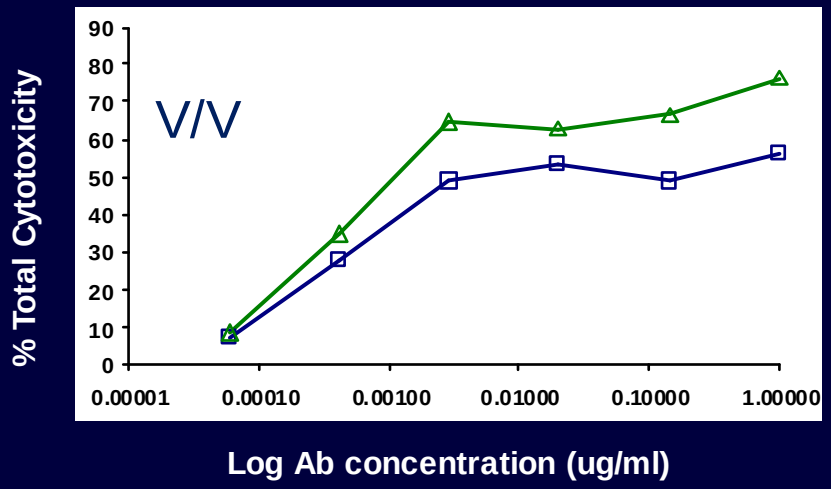
- Glycoengineered Fc domain
  Enhanced ADCC effect
- Modified elbow hinge
  Apoptosis induction

Mossner et al, Blood 2010

ADCC against WM cells for GA101 is greater among autologous NK cells genotyped for FCGR3A-158 F/F

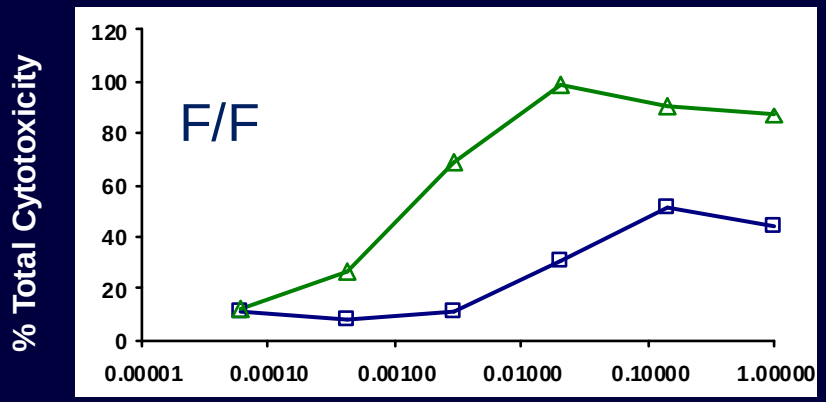
WM patient

FcγRIIIA-158 V/V



WM patient

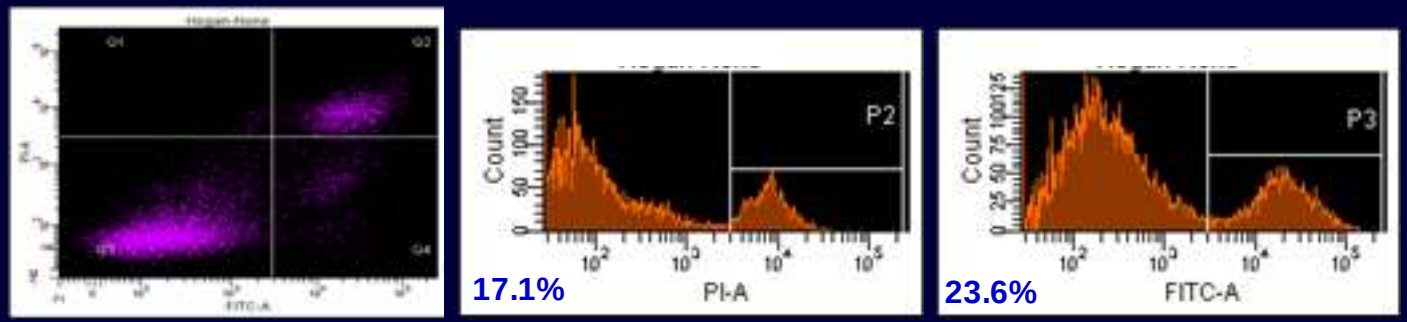
FcγRIIIA-158 F/F



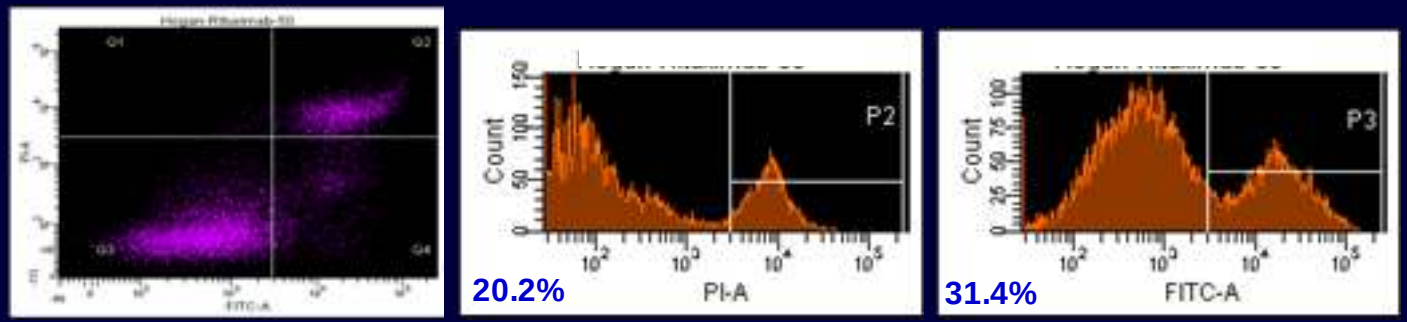
Yang et al, ASCO 2010

GA101 demonstrates greater direct killing vs. rituximab in BCWM.1 WM cells.

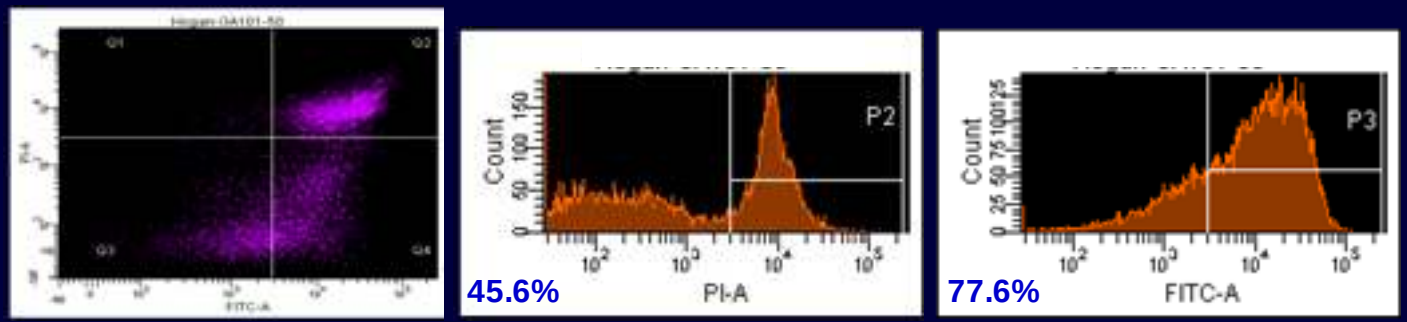
Untreated



Rituximab



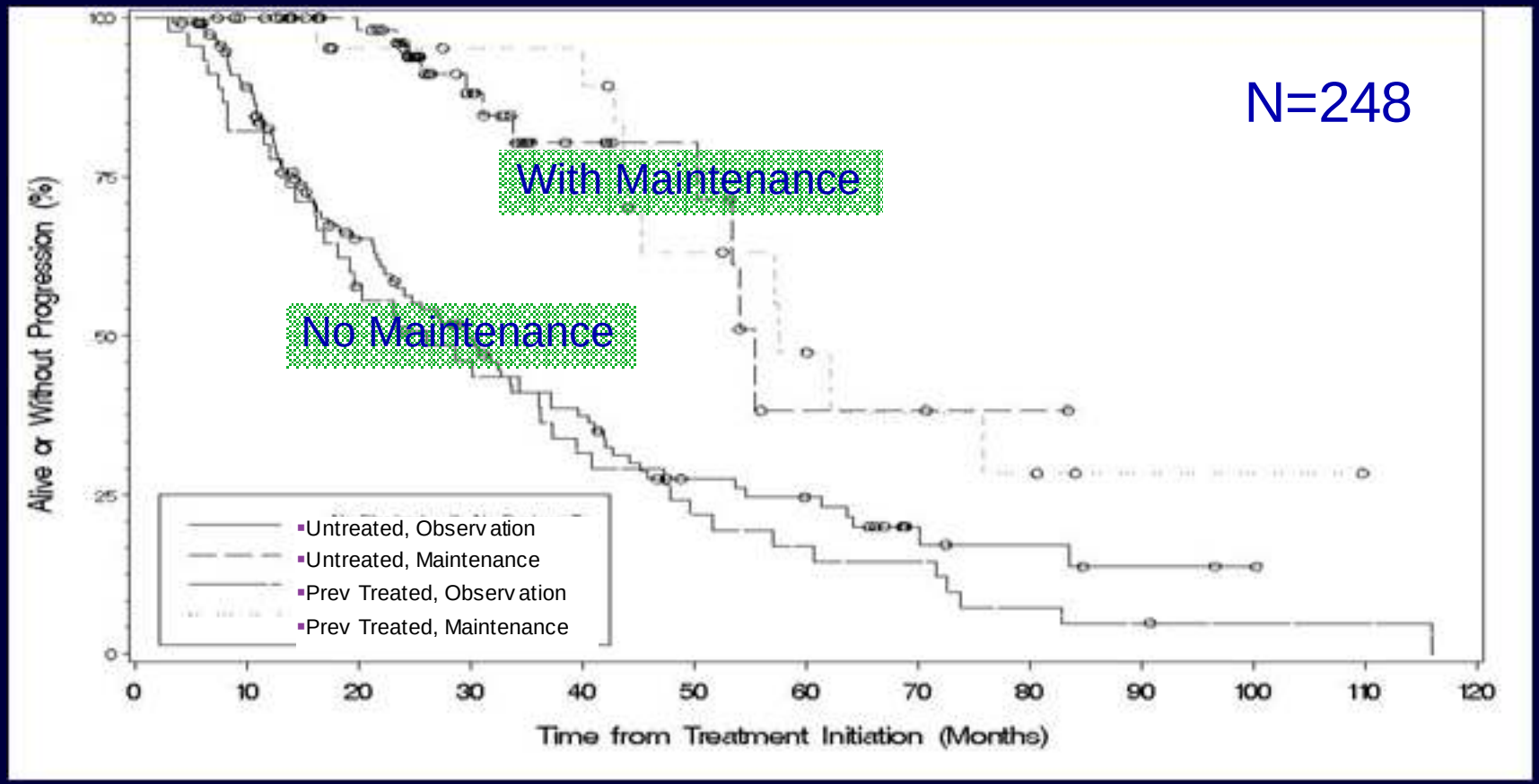
GA101



To Maintain or Not to Maintain?

Treon et al, BJH 2011

PFS in rituximab naïve WM patients who underwent observation or maintenance rituximab therapy.

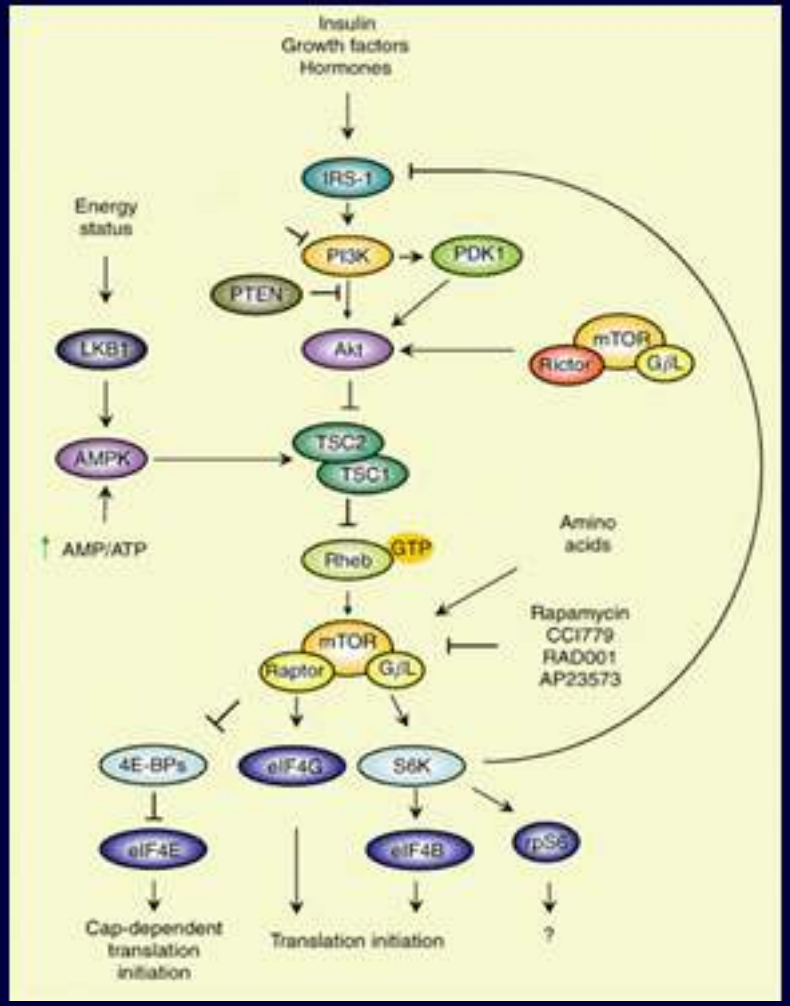


	Observation	Maintenance	p=
Untreated (Median PFS)	29.6 months	54.6 months	0.0001
Prev Treated (Median PFS)	25.6 months	56.7 months	0.0001

RAD001 in Relapsed/Refractory WM

- N = 50 (DFCI and Mayo)
- 10 mg QD
  - Reduce to 5 mg for AE
- Median prior therapies: 3
- Median IgM: 3330 mg/dL
- ORR: 72%
- Median response:

  NR (3-22+ mos)
- Grade ≥3 thrombocytopenia, pneumonitis, mucositis, and hyperglycemia.

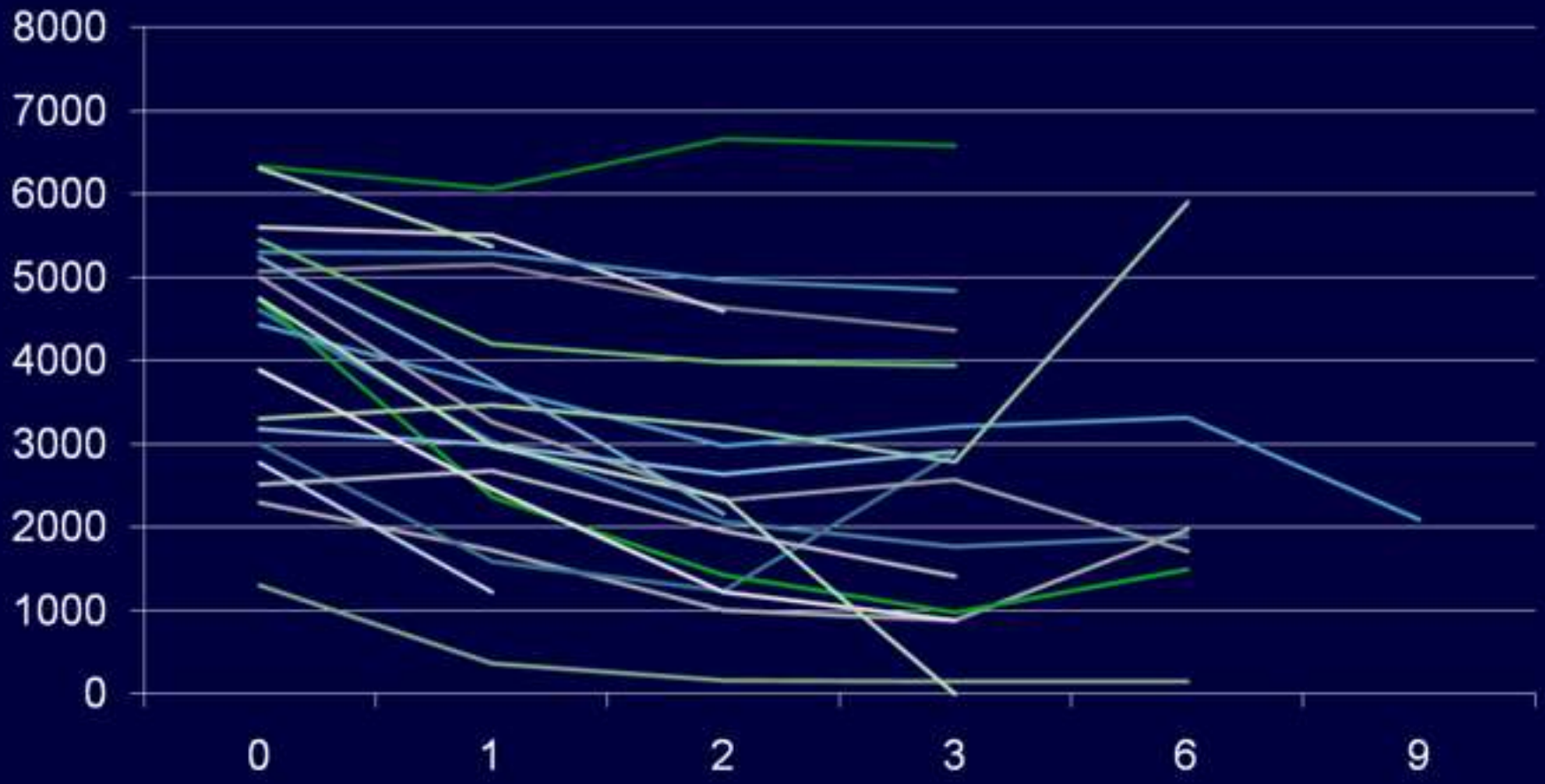


Ghobrial , Witzig et al, JCO 2010

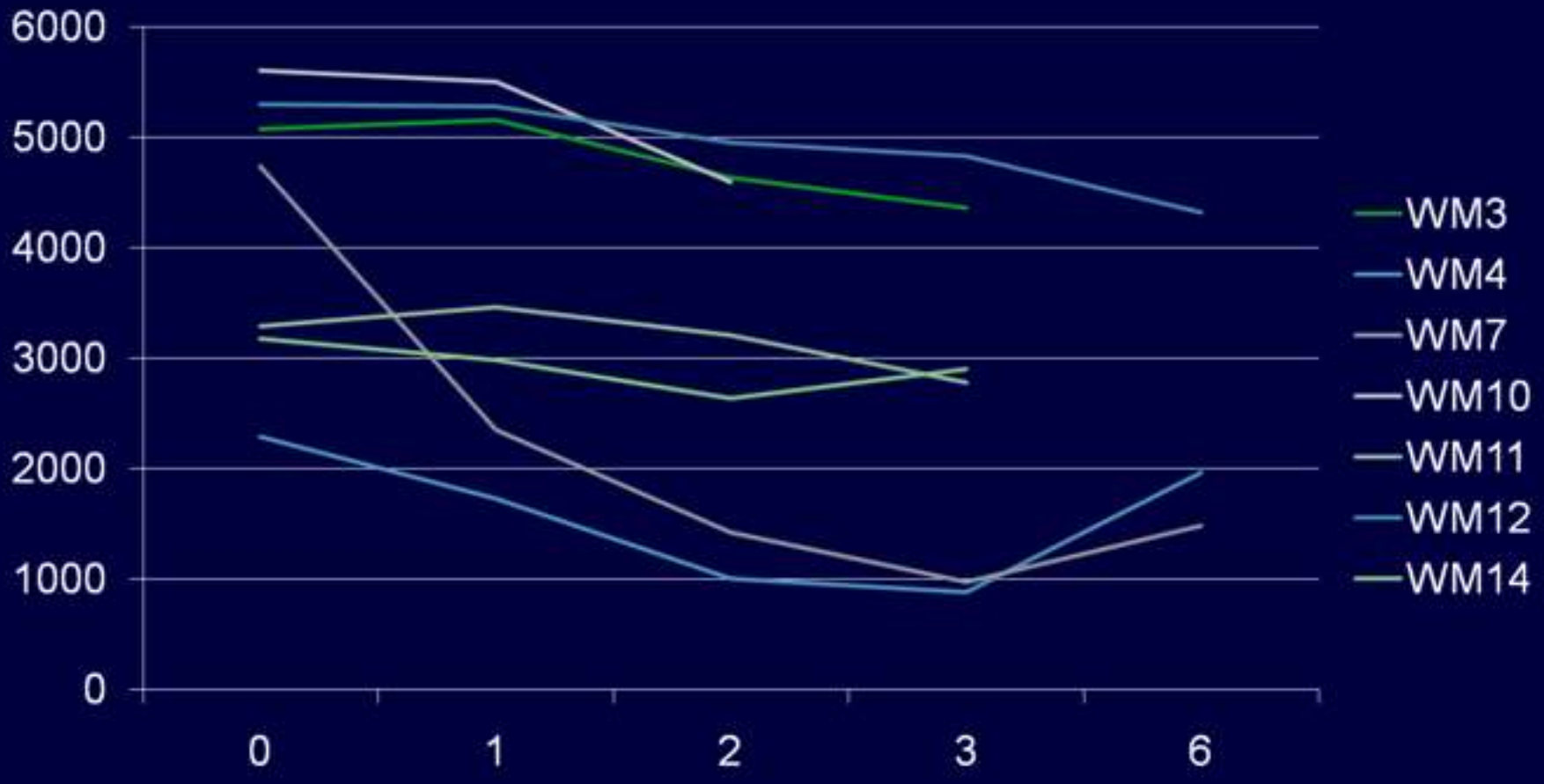
RAD001 for Primary Therapy of WM

- N = 60
- Eligibility: symptomatic, untreated WM
- Dose: 10 mg QD
  - Reduction to 7.5, 5.0 mg for AE
- Duration: 4 yrs to progression
- Primary endpoints: safety, ORR, and 2- and 4-yr PFS

IgM changes following RAD001 in untreated WM patients.



IgM discordance to WM BM disease involvement is common with RAD001

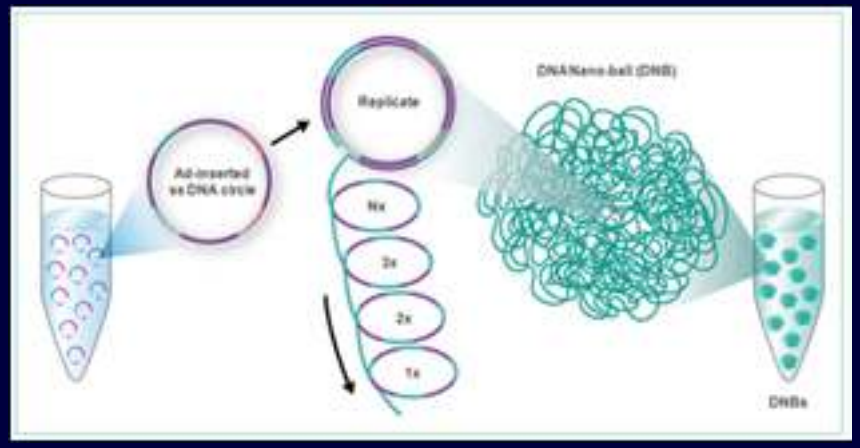


7 non-responders by serial BM biopsies despite reductions in sIgM.

Summary

- Familial disease predisposition is common in WM and effects treatment outcome.
- Bendamustine, Bortezomib Cyclophosphamide, and Thalidomide based rituximab therapies are active and can be considered in the upfront treatment of WM.
- Use of nucleoside analogues should be carefully considered due to potential long-term consequences.
- Better categorical responses are associated with improved progression free survival in rituximab naïve WM patients receiving rituximab based therapy, and reflect FCGR3A polymorphisms.
- IgM discordance is common with RAD001, and BMBx are important for serial response assessment.

Whole Genome Sequencing of WM Patients



- First 30 WM patients completed with tumor/normal pairing. Sporadic and Familial patients included
- Deep sequencing (i.e. > 60 X average coverage used).
- *Growth activating somatic mutation identified in 90% of WM patients, vs. 0% of MM patients. Targetable for therapy!!*

Manuscript in Review.

"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided."

Phillipus Aureolus Paracelsus

Acknowledgements

Dr. Irene Ghobrial (USA)
Prof. Pierre Morel (France)
Prof. Eva Kimby (Sweden)
Dr. Jeffrey Matous (Denver)
Dr. Herb Eradat (UCLA)
Dr. Stephanie Gregory (RUSH)
Dr. Ashraf Badros (UMD)
Dr. Ranjana Advani (Stanford Univ)
Dr. Leonard Heffner (Emory)
Dr. Sheeba Thomas (MD Anderson)

- Laboratory of Dr. Kenneth Anderson
  Constantine Mitsiades, Douglas McMillin
- Laboratory of Dr. Nikhil Munshi
- Laboratory of Dr. Steve Treon

Millennium Takeda
Celgene
Onyx
Novartis
Roche/Genentech
Biogen IDEC